COLESEVELAM HYDROCHLORIDE- colesevelam hydrochloride powder, for suspension
Glenmark Pharmaceuticals Inc.,USA

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use COLESEVELAM HYDROCHLORIDE FOR ORAL SUSPENSION safely and effectively. See full prescribing information for COLESEVELAM HYDROCHLORIDE FOR ORAL SUSPENSION. COLESEVELAM HYDROCHLORIDE for oral suspension
Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

Dosage and Administration (2.1) 05/2020
Warnings and Precautions (5.1) 05/2020

INDICATIONS AND USAGE

Colesevelam hydrochloride for oral suspension is a bile acid sequestrant indicated as an adjunct to diet and exercise to:

- reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia (1.1).
- reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) (1.1).

Limitations of Use (1.3):

- Do not use for treatment of type 1 diabetes or for diabetic ketoacidosis.
- The effect on cardiovascular morbidity and mortality has not been determined.
- Not studied in type 2 diabetes with a dipeptidyl peptidase 4 inhibitor.
- Not studied in Fredrickson Type I, III, IV, and V dyslipidemias.
- Not studied in children less than 10 years of age or in premenarchal girls.

DOSAGE AND ADMINISTRATION

- Obtain lipid parameters, including serum triglyceride (TG) levels, before starting colesevelam hydrochloride for oral suspension (2.1).
- The recommended dosage for adults and children 10 to 17 years old with primary hyperlipidemia is 3.75 grams daily or one 1.875 grams packet twice daily. Colesevelam hydrochloride for oral suspension should be taken as follows (2.2, 2.4):

For Oral Suspension
Take one 3.75 grams packet once daily or one 1.875 grams packet twice daily with a meal. To prepare, empty the entire contents of one packet into the glass or cup. Add ½ cup to 1 cup of water, fruit juice, or diet soft drinks. Stir well and drink.

DOSAGE FORMS AND STRENGTHS

- For Oral Suspension: 3.75 gram packet,1.875 gram packet (3)

CONTRAINDICATIONS

- Patients with serum triglyceride levels >500 mg/dL (4).
- Patients with a history of hypertriglyceridemia-induced pancreatitis (4).
- Patients with a history of bowel obstruction (4).

WARNINGS AND PRECAUTIONS

- *Hypertriglyceridemia and Pancreatitis:* Colesevelam hydrochloride can increase TG. Hypertriglyceridemia can cause acute pancreatitis. Monitor lipids, including TG. Instruct patients to discontinue colesevelam hydrochloride and seek prompt medical attention if the symptoms of acute pancreatitis occur (5.1).
- *Gastrointestinal Obstruction:* Cases of bowel obstruction have occurred. Colesevelam hydrochloride is

not recommended in patients with gastroparesis, other gastrointestinal motility disorders, and in those who have had major gastrointestinal tract surgery and who may be at risk for bowel obstruction (5.2).
- *Vitamin K or Fat-Soluble Vitamin Deficiencies:* Colesevelam hydrochloride may decrease absorption of fat-soluble vitamins. Patients with a susceptibility to deficiencies of vitamin K (e.g., patients on warfarin, patients with malabsorption syndromes) or other fat-soluble vitamins may be at increased risk. Patients on oral vitamin supplementation should take their vitamins at least 4 hours prior to colesevelam hydrochloride (5.3).
- *Drug Interactions:* Due to the potential for decreased absorption of other drugs that have not been tested for interaction, consider administering at least 4 hours prior to colesevelam hydrochloride (5.4, 7, 12.3).

ADVERSE REACTIONS

In clinical trials, the most common (incidence ≥2% and greater than placebo) adverse reactions with colesevelam hydrochloride included constipation, dyspepsia, and nausea (6.1).
To report SUSPECTED ADVERSE REACTIONS, contact Glenmark Pharmaceuticals Inc., USA at 1 (888) 721-7115 or FDA at 1-800-FDA-1088 or http://www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant use with colesevelam hydrochloride may decrease the exposure of the following drugs: Drugs with a narrow therapeutic index (e.g., cyclosporine), phenytoin, thyroid hormone replacement therapy, warfarin, oral contraceptives containing ethinyl estradiol and norethindrone, olmesartan medoxomil, and sulfonylureas (glimepiride, glipizide, glyburide). Administer these drugs 4 hours prior to colesevelam hydrochloride. For patients on warfarin, monitor International Normalized Ratio (INR) frequently during initiation then periodically (7.1).
Concomitant use with colesevelam hydrochloride may increase the exposure of the following drugs: Metformin extended release. Monitor patients' glycemic control (7.2).
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Primary Hyperlipidemia

Colesevelam hydrochloride for oral suspension is indicated as an adjunct to diet and exercise to reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia.

Colesevelam hydrochloride for oral suspension is indicated to reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) who are unable to reach LDL-C target levels despite an adequate trial of dietary therapy and lifestyle modification.

1.3 Limitations of Use

- Colesevelam hydrochloride for oral suspension should not be used for the treatment of type 1 diabetes or for the treatment of diabetic ketoacidosis.
- The effect of colesevelam hydrochloride for oral suspension on cardiovascular morbidity and mortality has not been determined.
- Colesevelam hydrochloride has not been studied in type 2 diabetes in combination with a dipeptidyl peptidase 4 inhibitor.
- Colesevelam hydrochloride for oral suspension has not been studied in Fredrickson

Type I, III, IV, and V dyslipidemias.
- Colesevelam hydrochloride for oral suspension has not been studied in children younger than 10 years of age or in premenarchal girls.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of Colesevelam Hydrochloride for Oral Suspension

Obtain lipid parameters, including triglyceride (TG) levels, before starting colesevelam hydrochloride for oral suspension. Colesevelam hydrochloride for oral suspension is contraindicated in patients with TG levels >500 mg/dL *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage in Primary Hyperlipidemia

The recommended dosage of colesevelam hydrochloride for oral suspension for adults and children 10 to 17 years old with primary hyperlipidemia is 3.75 grams daily or one 1.875 grams packet twice daily. Colesevelam hydrochloride for oral suspension should be taken as follows:

For Oral Suspension

1.875 gm – Take one packet twice daily

3.75 gm - Take one packet once daily.

2.3 Important Dosing Information for Primary Hyperlipidemia

Colesevelam hydrochloride for oral suspension can be dosed at the same time as a statin, or colesevelam hydrochloride for oral suspension and the statin can be dosed apart. Monitor lipid levels within 4 to 6 weeks after initiation of colesevelam hydrochloride for oral suspension.

2.4 Administration Instructions

For Oral Suspension

To prepare, empty the entire contents of one packet into a glass or cup. Add ½ to 1 cup (4 to 8 ounces) of water, fruit juice, or diet soft drinks. Stir well and drink. It is normal for the contents to appear cloudy and fully not dissolved. Take colesevelam hydrochloride for oral suspension with meals. Do not take colesevelam hydrochloride for oral suspension in its dry form. Due to tablet size, colesevelam hydrochloride for oral suspension is recommended for use in the pediatric population.

3 DOSAGE FORMS AND STRENGTHS

- Colesevelam hydrochloride for oral suspension: Citrus flavored, off-white to yellow granular powder packaged in single-dose packets: 3.75 gram single-dose packet, 1.875 gram single-dose packet.

4 CONTRAINDICATIONS

Colesevelam hydrochloride for oral suspension is contraindicated in patients with:

- Serum TG concentrations > 500 mg/dL *[see Warnings and Precautions (5.1)]*
- History of hypertriglyceridemia-induced pancreatitis *[see Warnings and Precautions (5.1)]*
- A history of bowel obstruction *[see Warnings and Precautions (5.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Hypertriglyceridemia and Pancreatitis

Colesevelam hydrochloride, like other bile acid sequestrants, can increase serum TG concentrations. Hypertriglyceridemia can cause acute pancreatitis.

Colesevelam hydrochloride had effects on serum TG (median increase 5% compared to placebo) in trials of patients with primary hyperlipidemia.

Obtain lipid parameters, including TG levels, before starting colesevelam hydrochloride and periodically thereafter. Colesevelam hydrochloride is contraindicated in patients with TG levels >500 mg/dL or patients with a history of hypertriglyceridemia-induced pancreatitis *[see Contraindications (4)]*. Patients with TG levels greater than 300 mg/dL could have greater increases in serum TG levels with colesevelam hydrochloride and may require additional TG monitoring. Instruct patients to discontinue colesevelam hydrochloride for oral suspension and seek prompt medical attention if the symptoms of acute pancreatitis occur (e.g., severe abdominal pain with or without nausea and vomiting). Discontinue colesevelam hydrochloride for oral suspension if TG levels exceed 500 mg/dL *[see Adverse Reactions (6.1)].*

5.2 Gastrointestinal Obstruction

Postmarketing cases of bowel obstruction have occurred with colesevelam hydrochloride *[see Adverse Reactions (6.2)]*. Because of its constipating effects, colesevelam hydrochloride is not recommended in patients with gastroparesis, other gastrointestinal motility disorders, and in those who have had major gastrointestinal tract surgery and who may be at risk for bowel obstruction. Colesevelam hydrochloride is contraindicated in patients with a history of bowel obstruction *[see Contraindications (4)]*. Instruct patients to promptly discontinue colesevelam hydrochloride and seek medical attention if severe abdominal pain or severe constipation occurs.

Because of the tablet size, colesevelam hydrochloride tablets can cause dysphagia or esophageal obstruction. For patients with difficulty swallowing tablets, use colesevelam hydrochloride for oral suspension.

5.3 Vitamin K or Fat-Soluble Vitamin Deficiencies

Colesevelam hydrochloride may decrease the absorption of fat-soluble vitamins A, D, E, and K. Patients with a susceptibility to deficiencies of vitamin K (e.g., patients on warfarin, patients with malabsorption syndromes) or other fat-soluble vitamins may be at increased risk when taking colesevelam hydrochloride.

Patients on oral vitamin supplementation should take their vitamins at least 4 hours prior

to colesevelam hydrochloride *[see Drug Interactions (7.1)]*.

5.4 Drug Interactions

Colesevelam hydrochloride reduces gastrointestinal absorption of some drugs. Administer drugs with a known interaction at least 4 hours prior to colesevelam hydrochloride *[see Drug Interactions (7)]*.

Due to the potential for decreased absorption of other drugs that have not been tested for interaction, especially those with a narrow therapeutic index, consider administering at least 4 hours prior to colesevelam hydrochloride *[see Clinical Pharmacology (12.3)].*

5.6 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular disease risk reduction with colesevelam hydrochloride.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypertriglyceridemia and Pancreatitis *[see Warnings and Precautions (5.1)]*
- Gastrointestinal Obstruction *[see Warnings and Precautions (5.2)]*
- Vitamin K or Fat-Soluble Vitamin Deficiencies *[see Warnings and Precautions (5.3)]*

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in clinical studies of another drug and may not reflect the rates observed in practice.

Primary Hyperlipidemia

In 7 double-blind, placebo-controlled clinical trials, 807 patients with primary hyperlipidemia (age range 18 to 86 years, 50% women, 90% Caucasians, 7% Blacks, 2% Hispanics, 1% Asians) and elevated LDL-C were treated with colesevelam hydrochloride 1.5 g/day to 4.5 g/day from 4 to 24 weeks (total exposure 199 patient-years).

Table 1: Clinical Studies of Colesevelam Hydrochloride for Primary Hyperlipidemia: Adverse Reactions Reported in ≥ 2% of Patients and More Commonly than in Placebo

	Colesevelam Hydrochloride N = 807	**Placebo N = 258**
Constipation	11%	7%
Dyspepsia	8.3%	3.5%
Nausea	4.2%	3.9%
Accidental injury	3.7%	2.7%
Asthenia	3.6%	1.9%
Pharyngitis	3.2%	1.9%

Flu syndrome	3.2%	3.1%
Rhinitis	3.2%	3.1%
Myalgia	2.1%	0.4%

Pediatric Patients 10 to 17 Years of Age

In an 8-week double-blind, placebo-controlled study, boys and post-menarchal girls, 10 to 17 years of age, with HeFH (n=194), were treated with colesevelam hydrochloride tablets (1.9 to 3.8 g, daily) or placebo tablets.

Table 2: Clinical Study of Colesevelam Hydrochloride for Primary Hyperlipidemia in HeFH Pediatric Patients: Adverse Reactions Reported in ≥2% of Patients and More Commonly than in Placebo

	Colesevelam Hydrochloride N = 129	**Placebo N = 65**
Nasopharyngitis	6.2%	4.6%
Headache	3.9%	3.1%
Fatigue	3.9%	1.5%
Creatine Phosphokinase Increase	2.3%	0%
Rhinitis	2.3%	0%
Vomiting	2.3%	1.5%

The reported adverse reactions during the additional 18-week open-label treatment period with colesevelam hydrochloride 3.8 g per day were similar to those during the double-blind period and included headache (7.6%), nasopharyngitis (5.4%), upper respiratory tract infection (4.9%), influenza (3.8%), and nausea (3.8%).

Hypertriglyceridemia

Colesevelam hydrochloride resulted in a median increase in serum TG of 5% compared to placebo (p=0.42) in a 24-week monotherapy lipid-lowering trial.

6.2 Post-marketing Experience

The following additional adverse reactions have been identified during post-approval use of colesevelam hydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse Reactions Resulting from Drug Interactions [see Drug Interactions (7)]:
Increased seizure activity or decreased phenytoin levels in patients receiving phenytoin, reduced International Normalized Ratio (INR) in patients receiving warfarin therapy, and elevated thyroid-stimulating hormone (TSH) in patients receiving thyroid hormone replacement therapy.
Gastrointestinal:
Bowel obstruction (in patients with a history of bowel obstruction or resection), dysphagia or esophageal obstruction (occasionally requiring medical intervention), fecal impaction, pancreatitis, abdominal distension, exacerbation of hemorrhoids,

and increased transaminases.
Laboratory Abnormalities:
Hypertriglyceridemia

7 DRUG INTERACTIONS

7.1 Colesevelam Hydrochloride Drug Interactions that Decrease the Exposure of the Concomitant Medication

Table 4 includes a list of drugs that decrease exposure of the concomitant medication when administered concomitantly with colesevelam hydrochloride and instructions for preventing or managing them.

Table 4: Colesevelam Hydrochloride Drug Interactions that Decrease the Exposure of the Concomitant Medication

Drugs with a Narrow Therapeutic Index	
Clinical Impact:	Concomitant use with colesevelam hydrochloride may decrease the exposure of the narrow therapeutic index drug. *In vivo* drug interactions studies showed a decrease in exposure of cyclosporine when coadministered with colesevelam hydrochloride *[see Clinical Pharmacology (12.3)].*
Intervention:	Administer the narrow therapeutic index drug at least 4 hours prior to colesevelam hydrochloride. Monitor drug levels when appropriate.
Examples:	Cyclosporine
Phenytoin	
Clinical Impact:	There have been postmarketing reports of increased seizure activity or decreased phenytoin levels in patients receiving phenytoin *[see Adverse Reactions (6.2)].*
Intervention:	Administer phenytoin 4 hours prior to colesevelam hydrochloride.
Thyroid Hormone Replacement Therapy	
Clinical Impact:	*In vivo* drug interactions studies showed a decrease in exposure of levothyroxine when coadministered with colesevelam hydrochloride *[see Clinical Pharmacology (12.3)].* There have been postmarketing reports of elevated thyroid-stimulating hormone (TSH) in patients receiving thyroid hormone replacement therapy *[see Adverse Reactions (6.2)].*
Intervention:	Administer thyroid hormone replacement therapy 4 hours prior to colesevelam hydrochloride.
Warfarin	
Clinical Impact:	There have been postmarketing reports of reduced INR in patients receiving warfarin therapy *[see Adverse Reactions (6.2)].*
Intervention:	Monitor INR frequently during colesevelam hydrochloride initiation then periodically thereafter.
Oral Contraceptives Containing Ethinyl Estradiol and Norethindrone	
Clinical Impact:	*In vivo* drug interactions studies showed a decrease in exposure of ethinyl estradiol and norethindrone when coadministered with colesevelam hydrochloride *[see Clinical Pharmacology (12.3)].*
Intervention:	Administer oral contraceptives containing ethinyl estradiol and norethindrone 4 hours prior to colesevelam hydrochloride.

Olmesartan Medoxomil	
Clinical Impact:	*In vivo* drug interactions studies showed a decrease in olmesartan medoxomil when coadministered with colesevelam hydrochloride *[see Clinical Pharmacology (12.3)].*
Intervention:	Administer olmesartan medoxomil 4 hours prior to colesevelam hydrochloride.
Sulfonylureas	
Clinical Impact:	*In vivo* drug interactions studies showed a decrease in sulfonylureas when coadministered with colesevelam hydrochloride *[see Clinical Pharmacology (12.3)].*
Intervention:	Administer sulfonylureas 4 hours prior to colesevelam hydrochloride.
Examples:	Glimepiride, glipizide, and glyburide
Oral Vitamin Supplements	
Clinical Impact:	Colesevelam hydrochloride may decrease the absorption of fat-soluble vitamins A, D, E, and K *[see Warnings and Precautions (5.3)].*
Intervention:	Patients on oral vitamin supplementation should take their vitamins at least 4 hours prior to colesevelam hydrochloride.

7.2 Colesevelam Hydrochloride Drug Interactions that Increase the Exposure of the Concomitant Medication

Table 5: Colesevelam Hydrochloride Drug Interactions that Increase the Exposure of the Concomitant Medication

Metformin Extended-Release (ER)	
Clinical Impact:	*In vivo* drug interactions studies showed an increase in metformin extended release (ER) when coadministered with colesevelam hydrochloride *[see Clinical Pharmacology (12.3)].*
Intervention:	Monitor patients' glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Colesevelam hydrochloride is not absorbed systemically following oral administration, and maternal use is not expected to result in fetal exposure to the drug. Limited available data on the use of colesevelam hydrochloride are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage. In animal reproduction studies, no evidence of either maternal or fetal toxicity was found in rats or rabbits exposed to colesevelam hydrochloride during the period of fetal organogenesis at 8 and 5 times, respectively, the maximum recommended human dose (MRHD) of 3.75 g/day, based on body surface area (mg/m^2). No adverse effects on offspring survival and development were observed in rats administered 5 times the MRHD *(see Data).* Colesevelam hydrochloride may decrease the absorption of fat-soluble vitamins *[see Warnings and Precautions (5.3)].* There are no data available on the effect of colesevelam hydrochloride on the absorption of fat-soluble vitamins in pregnant women. If the patient becomes pregnant while taking colesevelam hydrochloride, the patient should be advised of the lack of known clinical benefit with continued use during

pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

There are no adequate and well-controlled studies of colesevelam hydrochloride use in pregnant women. In the postmarketing setting there have been infrequent reports of pregnancy with use of colesevelam hydrochloride and a causal association with congenital anomalies has not been established.

Animal Data

In pregnant rats given dietary doses of 0.3, 1, 3 g/kg/day colesevelam hydrochloride from gestation days 7 through 17, no teratogenic effects were observed. Exposures at 3 g/kg/day were 8 times the human exposure at 3.75 g/day MRHD, based on body surface area (mg/m^2).

In pregnant rabbits given oral gavage doses of 0.1, 0.5, 1 g/kg/day colesevelam hydrochloride from gestation days 6 through 18, no teratogenic effects were observed. Exposures at 1 g/kg/day were 5 times the human exposure at 3.75 g/day MRHD, based on body surface area (mg/m^2).

In pregnant rats given oral gavage doses of 0.1, 0.3, 1 g/kg/day colesevelam hydrochloride from gestation day 6 through lactation day 21 (weaning), no adverse effects on survival and development were observed. Exposures at 1 g/kg/day were 5 times the human exposure at 3.75 g/day MRHD, based on body surface area (mg/m^2).

8.2 Lactation

Risk Summary

Colesevelam hydrochloride is not absorbed systemically by the mother following oral administration, and breastfeeding is not expected to result in exposure of the child to colesevelam hydrochloride.

8.3 Females and Males of Reproductive Potential

Contraception

Use of colesevelam hydrochloride may reduce the efficacy of oral contraceptives. Advise patients to take oral contraceptives at least 4 hours prior to taking colesevelam hydrochloride *[see Drug Interactions (7)].*

8.4 Pediatric Use

The safety and effectiveness of colesevelam hydrochloride as monotherapy or in combination with a statin were evaluated in children, 10 to 17 years of age, with HeFH *[see Clinical Studies (14.1)]*. The adverse reaction profile was similar to that of patients treated with placebo. In this limited controlled study, there were no significant effects on growth, sexual maturation, fat-soluble vitamin levels or clotting factors in the adolescent

boys or girls relative to placebo *[see Adverse Reactions (6.1)]*.

Due to tablet size, colesevelam hydrochloride for oral suspension is recommended for use in the pediatric population. Dose adjustments are not required when colesevelam hydrochloride is administered to children 10 to 17 years of age.

Colesevelam hydrochloride has not been studied in children younger than 10 years of age or in premenarchal girls.

8.5 Geriatric Use

Primary Hyperlipidemia

Of the 1350 patients enrolled in the hyperlipidemia clinical studies, 349 (26%) were ≥65 years old, and 58 (4%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

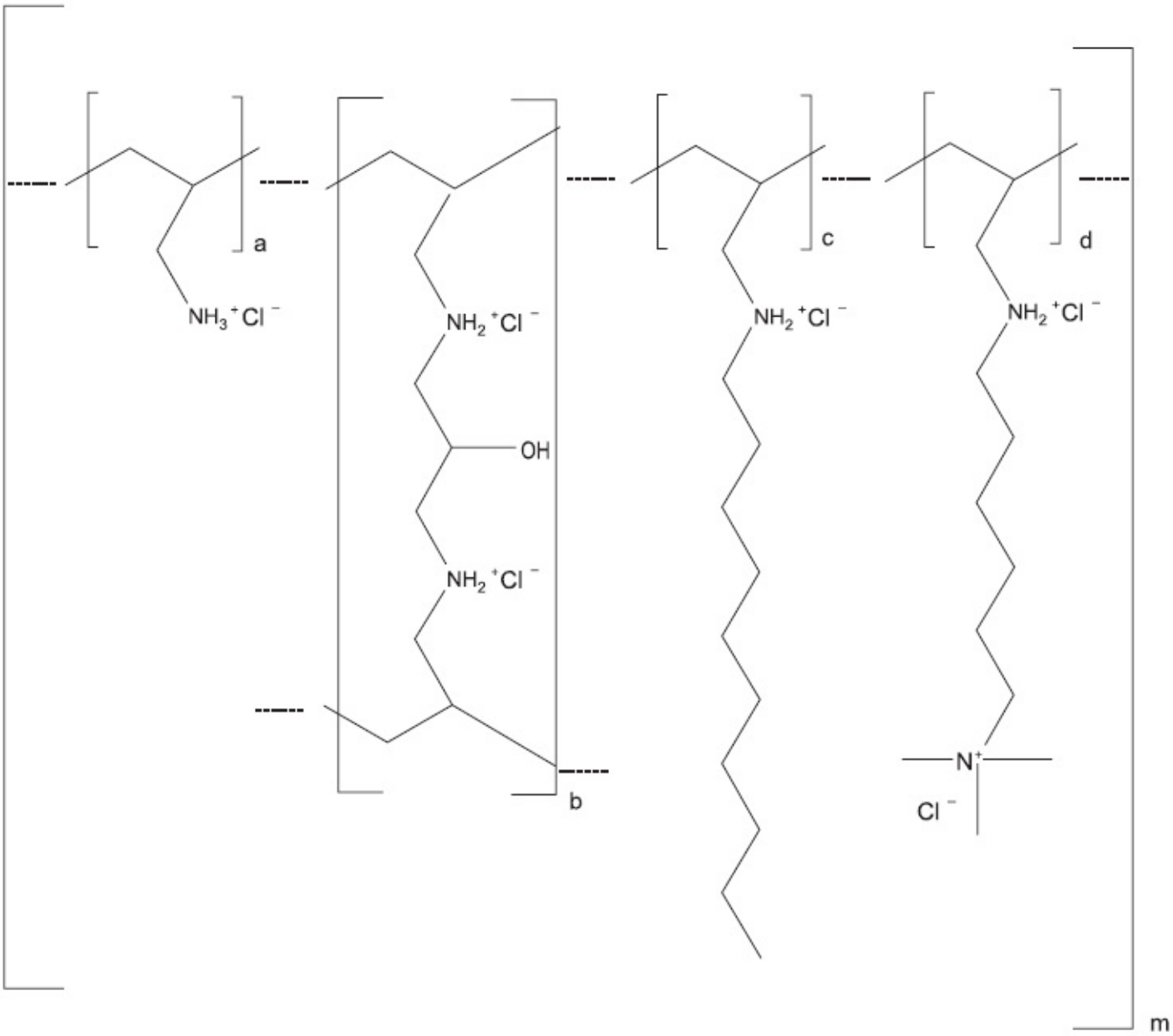
10 OVERDOSAGE

Colesevelam hydrochloride is not absorbed and the risk of systemic toxicity is low. Excessive doses of colesevelam hydrochloride may cause more severe local gastrointestinal effects (e.g., constipation).

11 DESCRIPTION

Colesevelam hydrochloride is a non-absorbed, polymeric, lipid-lowering agent for oral administration. Colesevelam hydrochloride is a high-capacity bile acid-binding molecule.

Colesevelam hydrochloride is poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide. The chemical name (IUPAC) of colesevelam hydrochloride is allylamine polymer with 1-chloro-2,3-epoxypropane, [6-(allylamino)-hexyl]trimethylammonium chloride and N-allyldecylamine, hydrochloride. The chemical structure of colesevelam hydrochloride is represented by the following formula:



wherein (a) represents allyl amine monomer units that have not been alkylated by either of the 1-bromodecane or (6-bromohexyl)-trimethylammonium bromide alkylating agents or cross-linked by epichlorohydrin; (b) represents allyl amine units that have undergone cross-linking with epichlorohydrin; (c) represents allyl amine units that have been alkylated with a decyl group; (d) represents allyl amine units that have been alkylated with a (6-trimethylammonium) hexyl group, and m represents a number ≥ 100 to indicate an extended polymer network. A small amount of the amines are dialkylated and are not depicted in the formula above. No regular order of the groups is implied by the structure; cross-linking and alkylation are expected to occur randomly along the polymer chains. A large amount of the amines are protonated. The polymer is depicted in the hydrochloride form; a small amount of the halides are bromide. Colesevelam hydrochloride is hydrophilic and insoluble in water.

Colesevelam hydrochloride for oral suspension is a citrus flavored off-white to yellow granular powder packaged in single-dose packets containing either 1.875 gram or 3.75 gram colesevelam hydrochloride. In addition, each packet contains the following inactive

ingredients: hydrochloric acid, hydroxypropyl cellulose, hypromellose, lemon flavor, magnesium trisilicate, mannitol, PB82 natural orange, simethicone emulsion 30%, sorbitol, and sucralose. Lemon flavor consists of flavoring agent and modified food starch. PB82 natural orange consists of flavoring agent and modified food starch.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Primary Hyperlipidemia: Colesevelam hydrochloride, the active pharmaceutical ingredient in colesevelam hydrochloride for oral suspension, is a non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption. As the bile acid pool becomes depleted, the hepatic enzyme, cholesterol 7-α-hydroxylase, is upregulated, which increases the conversion of cholesterol to bile acids. This causes an increased demand for cholesterol in the liver cells, resulting in the dual effect of increasing transcription and activity of the cholesterol biosynthetic enzyme, HMG-CoA reductase, and increasing the number of hepatic LDL receptors. These compensatory effects result in increased clearance of LDL-C from the blood, resulting in decreased serum LDL-C levels. Serum TG levels may increase or remain unchanged.

12.2 Pharmacodynamics

A maximum therapeutic response to the lipid-lowering effects of colesevelam hydrochloride was achieved within 2 weeks and was maintained during long-term therapy.

12.3 Pharmacokinetics

Absorption

Colesevelam hydrochloride is a hydrophilic, water-insoluble polymer that is not hydrolyzed by digestive enzymes and is not absorbed.

Distribution

Colesevelam hydrochloride is not absorbed, and therefore, its distribution is limited to the gastrointestinal tract.

Elimination

Metabolism

Colesevelam hydrochloride is not metabolized systemically and does not interfere with systemic drug-metabolizing enzymes such as cytochrome P450.

Excretion

In 16 healthy volunteers, an average of 0.05% of administered radioactivity from a single ^{14}C-labeled colesevelam hydrochloride dose was excreted in the urine.

Drug Interaction Studies

Drug interactions between colesevelam and concomitantly administered drugs were screened through *in vitro* studies and confirmed in *in vivo* studies. *In vitro* studies demonstrated that cephalexin, metformin, and ciprofloxacin had negligible binding to

colesevelam hydrochloride. Therefore, an *in vivo* pharmacokinetic interaction of colesevelam hydrochloride with these drugs is unlikely. Colesevelam hydrochloride was found to have no significant effect on the bioavailability of aspirin, atenolol, digoxin, enalapril, fenofibrate, lovastatin, metoprolol, phenytoin, pioglitazone, quinidine, rosiglitazone, sitagliptin, valproic acid, and warfarin. The results of additional *in vivo* drug interactions of colesevelam hydrochloride are presented in Table 6.

Table 6: Mean Change in Drug Exposure ($AUC_{0-\infty}$ and C_{max}) when Administered with Colesevelam Hydrochloride (3.75 g)*

Drug	**Dose**	**Co-administered**		**1 hr prior to Colesevelam Hydrochloride**		**4 hrs prior to Colesevelam Hydrochloride**	
		$AUC_{0-\infty}$	C_{max}	$AUC_{0-\infty}$	C_{max}	$AUC_{0-\infty}$	C_{max}
Cyclosporine	200 mg	-34%	-44%	N/A	N/A	N/A	N/A
Ethinyl Estradiol†	0.035 mg	-24%	-24%	-18%	-1%	-12%	0%
Glimepiride	4 mg	-18%	-8%	N/A	N/A	-6%	3%
Glipizide	20 mg	-12%	-13%	N/A	N/A	-4%	0%
Glyburide	3 mg	-32%	-47%	-20%	-15%	-7%	4%
Levothyroxine	600 mcg	-22%	-33%	6%	-2%	1%	8%
Metformin ER	1500 mg	44%	8%	N/A	N/A	N/A	N/A
Norethindrone†	1 mg	-1%	-20%	5%	-3%	6%	7%
Olmesartan Medoxomil	40 mg	-39%	-28%	N/A	N/A	-15%	-4%
Repaglinide	2 mg	-7%	-19%	-6%	-1%	N/A	N/A
Verapamil sustained-release	240 mg	-31%	-11%	N/A	N/A	N/A	N/A

* With verapamil, the dose of colesevelam hydrochloride was 4.5 g.

† Oral contraceptive containing norethindrone and ethinyl estradiol.

N/A – not available

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A 104-week carcinogenicity study with colesevelam hydrochloride was conducted in CD-1 mice, at oral dietary doses up to 3 g/kg/day. This dose was approximately 50 times the maximum recommended human dose of 4.5 g/day, based on body weight, mg/kg.

There were no significant drug-induced tumor findings in male or female mice. In a 104-week carcinogenicity study with colesevelam hydrochloride in Harlan Sprague-Dawley

rats, a statistically significant increase in the incidence of pancreatic acinar cell adenoma was seen in male rats at doses >1.2 g/kg/day (approximately 20 times the maximum human dose, based on body weight, mg/kg) (trend test only). A statistically significant increase in thyroid C-cell adenoma was seen in female rats at 2.4 g/kg/day (approximately 40 times the maximum human dose, based on body weight, mg/kg).

Mutagenesis

Colesevelam hydrochloride and 4 degradants present in the drug substance have been evaluated for mutagenicity in the Ames test and a mammalian chromosomal aberration test. The 4 degradants and an extract of the parent compound did not exhibit genetic toxicity in an *in vitro* bacterial mutagenesis assay in S. typhimurium and E. coli (Ames assay) with or without rat liver metabolic activation. An extract of the parent compound was positive in the Chinese Hamster Ovary (CHO) cell chromosomal aberration assay in the presence of metabolic activation and negative in the absence of metabolic activation. The results of the CHO cell chromosomal aberration assay with 2 of the 4 degradants, decylamine HCl and aminohexyltrimethyl ammonium chloride HCl, were equivocal in the absence of metabolic activation and negative in the presence of metabolic activation. The other 2 degradants, didecylamine HCl and 6-decylamino-hexyltrimethyl ammonium chloride HCl, were negative in the presence and absence of metabolic activation.

Impairment of Fertility

Colesevelam hydrochloride did not impair fertility in rats at doses up to 3 g/kg/day (approximately 50 times the maximum human dose, based on body weight, mg/kg).

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

Reproduction studies have been performed in rats and rabbits at doses up to 3 g/kg/day and 1 g/kg/day, respectively (approximately 50 and 17 times the maximum human dose, based on body weight, mg/kg) and have revealed no evidence of harm to the fetus due to colesevelam hydrochloride.

14 CLINICAL STUDIES

14.1 Primary Hyperlipidemia

Colesevelam hydrochloride reduces total cholesterol (TC), LDL-C, apolipoprotein B (Apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) when administered alone or in combination with a statin in patients with primary hyperlipidemia.

Approximately 1600 patients were studied in 9 clinical trials with treatment durations ranging from 4 to 50 weeks. With the exception of one open-label, uncontrolled, long-term extension study, all studies were multicenter, randomized, double-blind, and placebo-controlled. A maximum therapeutic response to colesevelam hydrochloride was achieved within 2 weeks and was maintained during long-term therapy.

Monotherapy

In a study in patients with LDL-C between 130 mg/dL and 220 mg/dL (mean 158 mg/dL), colesevelam hydrochloride was given for 24 weeks in divided doses with the morning and evening meals.

As shown in Table 7, the mean LDL-C reductions were 15% and 18% at the 3.8 g and 4.5 g doses. The respective mean TC reductions were 7% and 10%. The mean Apo B reductions were 12% in both treatment groups. Colesevelam hydrochloride at both doses increased HDL-C by 3%. Increases in TG of 9 to 10% were observed at both colesevelam hydrochloride doses, but the changes were not statistically different from placebo.

Table 7: Response to Colesevelam Hydrochloride Monotherapy in a 24-Week Trial-Percent Change in Lipid Parameters from Baseline

Grams/Day	N	TC	LDL-C	Apo B	HDL-C*	Non-HDL-C	TG*
Placebo	88	+1	0	0	–1	+1	+5
3.8 g (6 tablets)	95	–7†	–15†	–12†	+3†	–10†	+10
4.5 g (7 tablets)	94	–10†	–18†	–12†	+3	–13†	+9

* Median % change from baseline

† $p<0.05$ for lipid parameters compared to placebo, for Apo B compared to baseline.

In a study in 98 patients with LDL-C between 145 mg/dL and 250 mg/dL (mean 169 mg/dL), colesevelam hydrochloride 3.8 g was given for 6 weeks as a single dose with breakfast, as a single dose with dinner, or as divided doses with breakfast and dinner. The mean LDL-C reductions were 18%, 15%, and 18% for the 3 dosing regimens, respectively. The reductions with these 3 regimens were not statistically different from one another.

Combination Therapy

Co-administration of colesevelam hydrochloride and a statin (atorvastatin, lovastatin, or simvastatin) in 3 clinical studies demonstrated an additive reduction of LDL-C. The mean baseline LDL-C was 184 mg/dL in the atorvastatin study (range 156 to 236 mg/dL), 171 mg/dL in the lovastatin study (range 115 to 247 mg/dL), and 188 mg/dL in the simvastatin study (range 148 to 352 mg/dL). As demonstrated in Table 8, colesevelam hydrochloride doses of 2.3 g to 3.8 g resulted in an additional 8% to 16% reduction in LDL-C above that seen with the statin alone.

Table 8: Response to Colesevelam Hydrochloride in Combination with Atorvastatin, Simvastatin, or Lovastatin-Percent Change in Lipid Parameters

Dose/Day	N	TC	LDL-C	Apo B	HDL-C*	Non-HDL-C	TG*
Atorvastatin Trial (4-week)							
Placebo	19	+4	+3	–3	+4	+4	+10
Atorvastatin 10 mg	18	–27†	–38†	–32†	+8	–35†	–24†
Colesevelam Hydrochloride 3.8 g/ Atorvastatin 10 mg	18	–31†	–48†	–38†	+11	–40†	–1
Atorvastatin 80 mg	20	–39†	–53†	–46†	+6	–50†	–33†

Simvastatin Trial (6-week)							
Placebo	33	–2	–4	–4†	–3	–2	+6†
Simvastatin 10 mg	35	–19†	–26†	–20†	+3†	–24†	–17†
Colesevelam Hydrochloride 3.8 g/ Simvastatin 10 mg	34	–28†	–42†	–33†	+10†	–37†	–12†
Simvastatin 20 mg	39	–23†	–34†	–26†	+7†	–30†	–12†
Colesevelam Hydrochloride 2.3 g/ Simvastatin 20 mg	37	–29†	–42†	–32†	+4†	–37†	–12†
Lovastatin Trial (4-week)							
Placebo	26	+1	0	0	+1	+1	+1
Lovastatin 10 mg	26	–14†	–22†	–16†	+5	–19†	0
Colesevelam Hydrochloride 2.3 g/ Lovastatin 10 mg Together	27	–21†	–34†	–24†	+4	–27†	–1
Colesevelam Hydrochloride 2.3 g/ Lovastatin 10 mg	23	–21†	–32†	–24†	+2	–28†	–2
Apart							

* Median % change from baseline.

† $p<0.05$ for lipid parameters compared to placebo, for Apo B compared to baseline

In all 3 studies, the LDL-C reduction achieved with the combination of colesevelam hydrochloride and any given dose of statin therapy was statistically superior to that achieved with colesevelam hydrochloride or that dose of the statin alone. The LDL-C reduction with atorvastatin 80 mg was not statistically significantly different from the combination of colesevelam hydrochloride 3.8 g and atorvastatin 10 mg.

Pediatric Therapy

The safety and efficacy of colesevelam hydrochloride in pediatric patients were evaluated in an 8-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study followed by an open-label phase, in 194 boys and postmenarchal girls 10 to 17 years of age (mean age 14.1 years) with HeFH, taking a stable dose of an FDA-approved statin (with LDL-C >130 mg/dL) or naïve to lipid-lowering therapy (with LDL-C >160 mg/dL). This study had 3 periods: a single-blind, placebo stabilization period; an 8-week, randomized, double-blind, parallel-group, placebo-controlled treatment period; and an 18-week, open-label treatment period. Forty-seven (24%) patients were taking statins and 147 (76%) patients were statin-naïve at screening. The mean baseline LDL-C at Day 1 was approximately 199 mg/dL.

During the double-blind treatment period, patients were assigned randomly to treatment: colesevelam hydrochloride 3.8 g/day (n=64), colesevelam hydrochloride 1.9 g/day (n=65), or placebo (n=65). In total, 186 patients completed the double-blind treatment period. After 8 weeks of treatment, colesevelam hydrochloride 3.8 g/day significantly decreased plasma levels of LDL-C, non-HDL-C, TC, and Apo B and significantly increased HDL-C. A moderate, non-statistically significant increase in TG was

observed versus placebo (Table 9).

Table 9: Response to Colesevelam Hydrochloride 3.8 g Compared to Placebo in Pediatric Patients 10 to 17 Years of Age – Mean Percent Change in Lipid Parameters from Baseline to Week 8

Treatment Difference	TC (N=128)	LDL-C (N=128)	Apo B (N=124)	HDL-C (N=128)	Non-HDL-C (N=128)	TG* (N=128)
Colesevelam Hydrochloride 3.8 g vs Placebo	-7†	-13†	-8†	+6†	–11†	+5

* For triglycerides, median % change from baseline.

†p≤0.05 for lipid parameters compared to placebo

Values represent LS mean. Only patients with values at both study baseline and endpoint are included in this table. Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.

Results were based on the ITT population with LOCF.

During the open-label treatment period patients were treated with colesevelam hydrochloride 3.8 g/day. In total, 173 (89%) patients completed 26 weeks of treatment. Results at Week 26 were consistent with those at Week 8.

16 HOW SUPPLIED/STORAGE AND HANDLING

Colesevelam hydrochloride for oral suspension contains a citrus flavored off-white to yellow granular powder. Colesevelam hydrochloride for oral suspension is available as follows:

- **1.875 gram**
  NDC 68462-619-60 1 box of 60 single-dose packets
  Note to Pharmacists: do not dispense contents separately; dispense as 1 box
- **3.75 gram**
  NDC 68462-620-30 1 box of 30 single-dose packets
  Note to Pharmacists: do not dispense contents separately; dispense as 1 box

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Hypertriglyceridemia and Pancreatitis

Inform patients that colesevelam hydrochloride may increase their serum triglycerides which can lead to hypertriglyceridemia and pancreatitis. Instruct patients to discontinue colesevelam hydrochloride and seek prompt medical attention if the symptoms of acute pancreatitis occur (e.g., severe abdominal pain with or without nausea and vomiting)

[see Warnings and Precautions (5.1)].

Gastrointestinal

Inform patients that colesevelam hydrochloride may cause bowel obstruction. Instruct patients to promptly discontinue colesevelam hydrochloride and seek medical attention if severe abdominal pain or severe constipation occurs *[see Warnings and Precautions (5.2)].*

Drug and Vitamin interactions

Advise patients that colesevelam hydrochloride has drug interactions, and colesevelam hydrochloride may decrease the absorption of fat-soluble vitamins A, D, E, and K. Instruct patients to take oral vitamins at least 4 hours prior to colesevelam hydrochloride. Instruct patients to inform their physician about all the drugs and vitamins that they are prescribed or take over the counter *[see Warnings and Precautions (5.3) and Drug Interactions (7)].*

Hypertriglyceridemia and Cardiovascular Disease

Inform patients that colesevelam hydrochloride may increase serum triglycerides and that the long-term effect of hypertriglyceridemia on the risk of coronary artery disease is uncertain *[see Warnings and Precautions (5.1)].*

Administration *[see Dosage and Administration (2.4)]*

For Oral Suspension

Instruct patients to empty the entire contents of one packet into a glass or cup and add ½ cup to 1 cup (4 to 8 ounces) of water, fruit juice, or diet soft drinks. Stir well and drink. Advise patients to take colesevelam hydrochloride oral suspension with meals. Advise patient to not take colesevelam hydrochloride oral suspension in its dry form.

Females of Reproductive Potential

Advise females of reproductive potential that colesevelam hydrochloride may reduce the effectiveness of oral contraceptives, and to take oral contraceptives at least 4 hours before taking colesevelam hydrochloride *[see Drug Interactions (7.1) and Use in Specific Populations (8.3)].*

Manufactured by:

Glenmark Pharmaceuticals Limited

Colvale-Bardez, Goa 403 513, India

Manufactured for:

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Mahwah, NJ 07430

Questions? 1 (888) 721-7115

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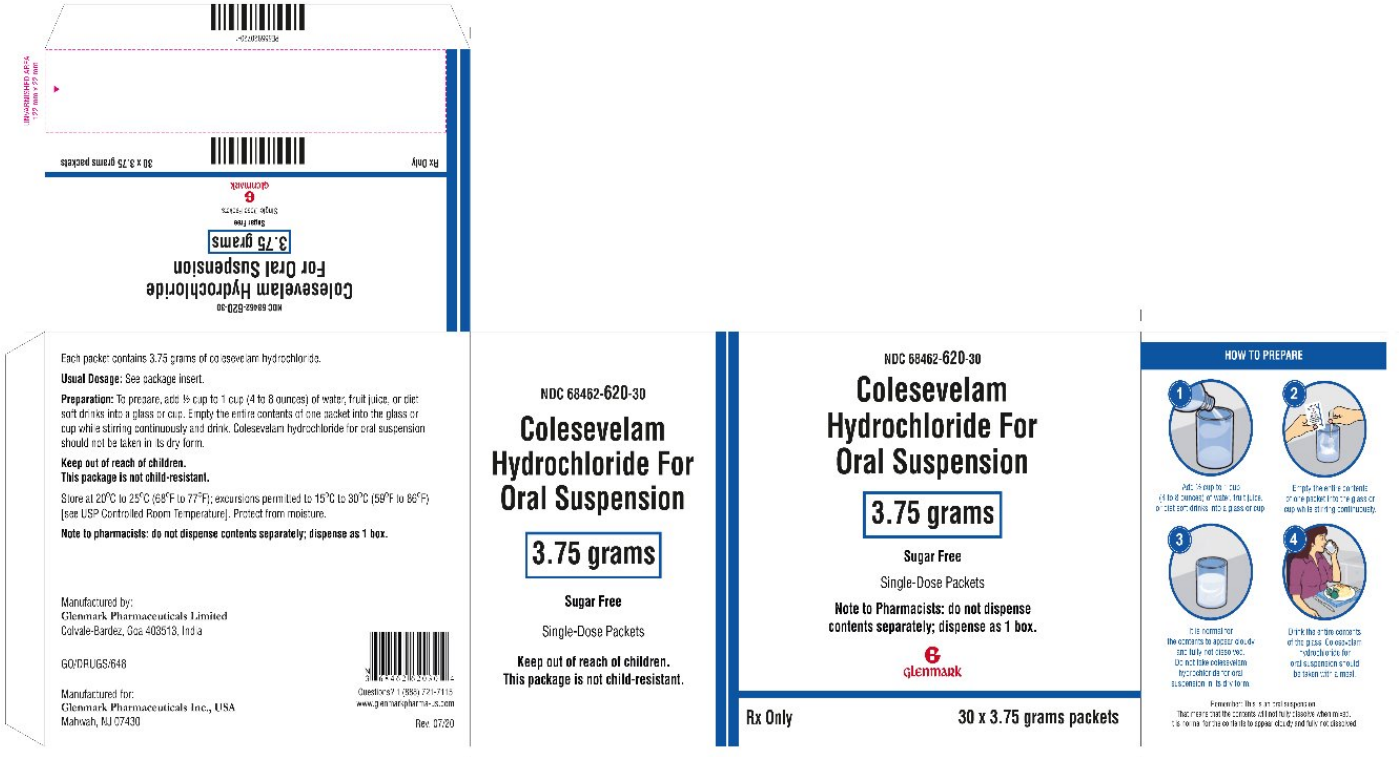
March 2021

PRINCIPAL DISPLAY PANEL

NDC 68462-620-30
Colesevelam Hydrochloride for Oral Suspension
3.75 gram



COLESEVELAM HYDROCHLORIDE

colesevelam hydrochloride powder, for suspension

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68462-620
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
COLESEVELAM HYDROCHLORIDE (UNII: P4SG24W5Q) (COLESEVELAM - UNII:1XU104G55N)	COLESEVELAM HYDROCHLORIDE	3.75 g

Inactive Ingredients

Ingredient Name	Strength
MAGNESIUM TRISILICATE (UNII: C2E1CI501T)	
MANNITOL (UNII: 3OWL53L36A)	
SORBITOL (UNII: 506T60A25R)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SUCRALOSE (UNII: 96K6UQ3ZD4)	
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
LEMON (UNII: 24RS0A988O)	
ORANGE (UNII: 5EVU04N5QU)	
MODIFIED CORN STARCH (1-OCTENYL SUCCINIC ANHYDRIDE) (UNII: 461P5CJN6T)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	

Product Characteristics

Color	YELLOW (off-white to yellow)	**Score**	
Shape		**Size**	
Flavor	CITRUS	**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68462-620-30	30 in 1 BOX	07/16/2018	
1		1 in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202190	07/16/2018	

Labeler - Glenmark Pharmaceuticals Inc.,USA (130597813)

Establishment

Name	Address	ID/FEI	Business Operations
Glenmark Pharmaceuticals Limited		677318665	ANALYSIS(68462-620) , MANUFACTURE(68462-620)

Revised: 3/2021 Glenmark Pharmaceuticals Inc.,USA